

The mystery of Traditional Chinese Medicine has been attracting people for years. Acupuncture, ranked among the most common services of Complementary and Alternative Medicine, has recently gained a lot of interest in the scientific world. Contemporary researchers have been continuously trying to shed light on its possible mechanism of action in human organism. Numerous studies pertaining to acupuncture's application in cancer symptoms or treatment-related side effects management have already been published. Moreover, since the modern idea of acupuncture's immunomodulating effect seems to be promising, scientists have propounded a concept of its potential application as part of direct anti-tumor therapy. In our previous study we summarized possible use of acupuncture in management of cancer symptoms and treatment-related ailments, such as chemotherapy-induced nausea and vomiting, pain, xerostomia, vasomotor symptoms, neutropenia, fatigue, anxiety, insomnia, lymphoedema after mastectomy and peripheral neuropathy. This article reviews the studies concerning acupuncture as a possible tool in modern anticancer treatment.

Key words: acupuncture, anticancer treatment, cancer, complementary treatment, therapy.

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Acupuncture as anticancer treatment?

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Introduction

Complementary and alternative medicine (CAM) is defined by the National Center for Complementary and Alternative Medicine as a heterogeneous group comprised of a wide array of medical services that are not considered conventional medicine [1]. The use of CAM is widespread and increasing [2], hence the number of studies concerning its possible application in everyday clinical practice is also on the rise [3]. Acupuncture, subsumed under CAM, is one of the world's oldest medical procedures [4] and has gained a lot of interest and appreciation over the years [5]. The popularity of this method is continuously increasing [6]. It has been nearly two decades now since acupuncture was, for the first time, introduced in oncology as a possible tool in care of cancer patients [7]. A lot has been written about its possible application as supportive therapy in the oncology field and that issue was discussed in detail in the preview article published by our group [8]. Additionally, some publications suggest that acupuncture can possibly be part of a direct anti-tumor therapy, mainly due to its immunomodulating effect [9, 10]. This review, as a continuation of the previously published study, is focused on the literature concerning acupuncture as antitumor therapy.

Methods

The material for the article was obtained from the literature search performed independently by two authors, in Medline/PubMed database (from 1990 to July 2014), the Cochrane Library (up to July 2014) and UpToDate. Following key words (in various combinations and forms) were used: 'acupuncture', 'CAM', 'immunomodulating effect', 'NK cell', 'activity', 'modulation', 'interferon gamma', 'complementary', 'anti-tumor', 'therapy', 'cancer', 'anticancer', 'treatment', 'oncology', 'application', 'electro-acupuncture', 'tumor volume', 'growth inhibition', 'immunotherapy', 'tumor response enhancement'. The foregoing phrases generated from several up to over 1100 results, depending on the source and specificity of searched issue (e.g. 'acupuncture' AND 'cancer' gives 501 results in Cochrane Library and 1153 in PubMed, whereas 'acupuncture' AND 'anticancer' generates 3 and 21 respectively). The 'RELATED CITATION' module in PubMed database was used in order to find additional articles. Only publications presenting acupuncture's direct or indirect anticancer effect were included. The results of studies based on animal model as well as human trials were analyzed. The ClinicalTrials.gov was searched to find information about currently ongoing clinical trials. Both full articles and abstracts were taken into consideration.

Possible mechanisms of anticancer activity

'The acupuncture immuno-enhancement hypothesis'

According to this theory, acupuncture enhances anticancer immunity of the human body by natural killer (NK) cells stimulation [11]. This hypothesis seems to be interesting since NK cells play a key role in regulating anticancer immune function and directly killing cancer cells [12]. NK cells use

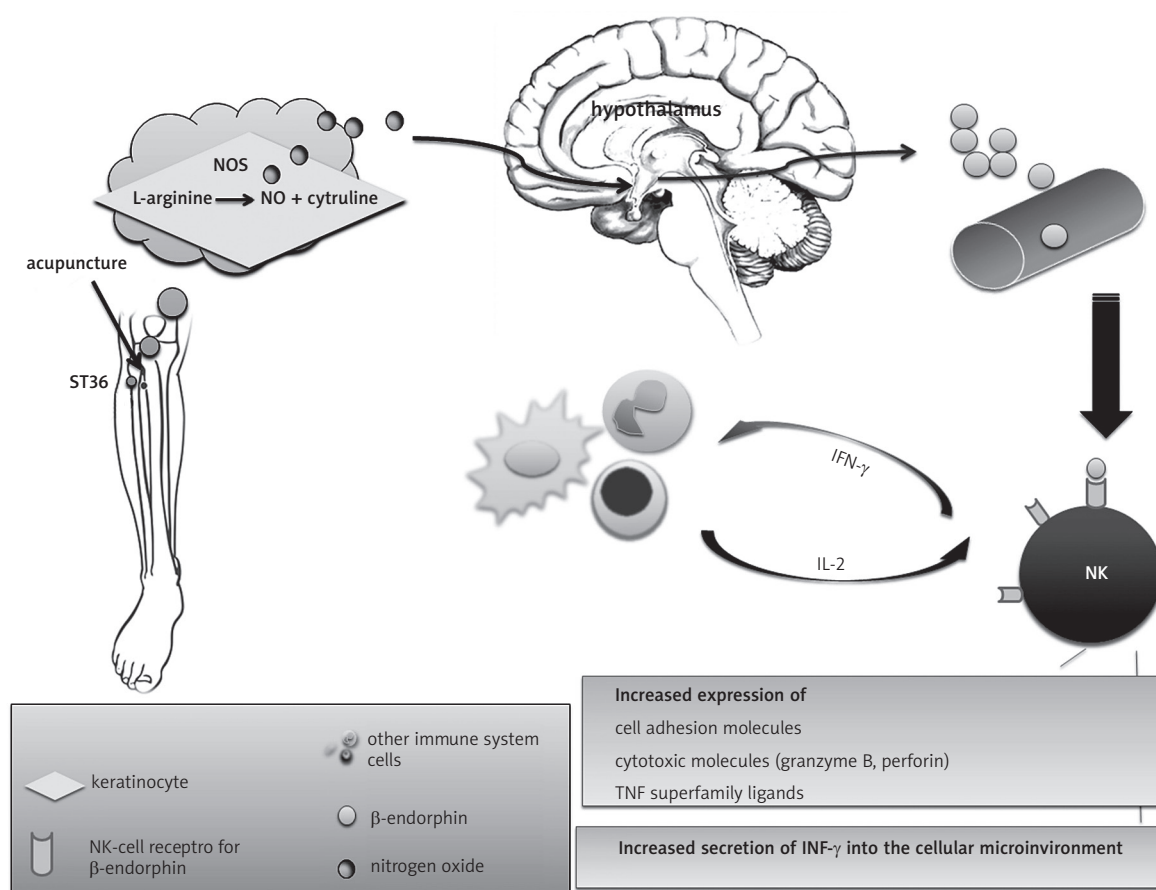
two mechanisms to kill cancer cells. The first one (secretory-cytotoxic mechanism) is mediated by the secreted cytolytic perforins and granzymes B (serine proteases), which damage deoxyribonucleic acid (DNA). The second one (non-secretory apoptotic mechanism) involves direct induction of apoptosis and is mediated by Tumor Necrosis Factor (TNF) family ligands located on NK cells membrane, e.g. Fas ligand (FasL). The second mechanism, which is more efficient and operative against all types of cancer cells, seems to be the major tool of NK cells activity [13–15]. Thanks to these efficient and highly selective killing strategies, NK cells are capable of detecting and eliminating newly formed and blood-borne cancer cells, and prevent the development of both primary tumors and their metastases [11].

The majority of the researches carried out so far on immunomodulatory effects of acupuncture have been focused on the stimulation of ST-36 acupoint, located on the pathway of the stomach meridian (Zusanli point, which is located 5 cm below the patella and 2 cm lateral of the anterior crest of

the tibialis anterior muscle) [16]. Figure 1 presents hypothetical mechanism of acupuncture's effect on immune system.

Considering researchers' findings concerning the fact that acupuncture increases cytotoxic NK cells activity, it is intriguing to notice acupuncture' indirect effect on activity of antigen presenting cells (APC), especially on dendritic cells (DCs). These cells transform antigens from tumor dead cells and, presenting them to lymphocytes T, trigger initiation of the adaptive immune response [17]. DCs have also the ability to directly, selectively and effectively kill tumor cells through apoptosis by the engagement of ligands of TNF receptor family with the corresponding cancer cell receptors [18].

NK cells play an additional immunoregulatory function as they are capable of stimulating DCs, initiating their maturation in the bone marrow and significantly increasing their ability to produce pro-inflammatory cytokines and induce immune response mediated by T1 helper cells (Th1) and cytotoxic T lymphocytes (Tc) [19]. NK cells and DCs interactions are triggered by receptors and ligands of the TNF family receptors [20]. Increased NK cells efficacy in killing trans-



Puncture of ST-36 point induces NOS in the keratinocytes, which results in increased concentration of NO. NO transmits signal to the appropriate neural centers located in the brain, including the lateral hypothalamic field. This leads to the production of β -endorphin in this area that is followed by increased β -endorphin peripheral blood concentration. β -endorphins, binding to opioid NK-cell membrane receptors, activate NK cells and thus stimulate IFN- γ production. IFN- γ influences other immune system cells that produce IL-2, which is a strong NK cells stimulator.

NOS – nitric oxide synthase; NO – nitric oxide; NK – natural killer; IFN- γ – interferon γ ; IL-2 – interleukin 2

Fig. 1. Hypothetical model explaining how acupuncture stimulates the immune system (based on [11])

Table 1. Summary of possible immunomodulating effects of acupuncture

Possible immunomodulating effects of acupuncture	Results	Ref.
NK cell activation	– direct antitumor activity through both secretory and non-secretory mechanism of killing cancer cells – induction of the secondary adaptive immune response by DCs and T lymphocytes	[14, 17, 19, 20]
<i>SPI1</i> pathway activation	– bone marrow stem cells stimulation – proliferation and maturation of the immune system cells	[24]
Increased IL-2 level	– NK cells stimulation – expression of 1NKp44 receptor on NK-cell surface	[25, 26]
NO synthesis	– NK cells activation – induction of NK cells proliferation	[27]
Increased endogenous B-endorphin	IFN- γ synthesis	[28]
Increased IFN- γ level	Mediates NK cell activity: – increased expression of TNF superfamily ligands and NK cells receptors – stimulate secretion of cytokines through other immune cells	[27, 29, 30]

¹NKp44: NK-cell surface receptor, one of the major receptors responsible for triggering NK cell cytotoxic activity [26]

NK cell – natural killer cell; DC – dendritic cell; *SPI1* – *Spi-1* proto-oncogene; IL – interleukin; NO – nitrogen oxide; IFN- γ – interferon γ ; TNF – tumor necrosis factor

Table 2. Examples of studies concerning acupuncture's immunomodulating effects

Study type	Results	Ref.
Animal model	Mice with transplanted mammary cancer – significantly increased NK cell activity in acupunctured group in comparison to controls ($p < 0.01$) – higher degree of lymphocytic infiltration of tumor ($p < 0.05$)	[9]
Animal model	– increased NK activity ($p < 0.05$) and level of IFN- γ ($p < 0.05$) in acupunctured group – no significant difference in NK splenic population	[28]
Animal model	– significantly enhanced NK cell splenic cytotoxicity ($p < 0.001$) – increased level of IFN- γ and IL-2 in comparison to non-acupunctured group ($p < 0.01$) – positive correlation between NK cells cytotoxicity and the level of each cytokine was observed ($p < 0.01$)	[29]
Case series	60 patients with metastatic colorectal cancer – significantly increased level of NK cells in peripheral blood after acupuncture (patients with metastatic colorectal cancer)	[10]
Case series	17 healthy volunteers – increase in IFN- γ serum level and markers of peripheral NK cells activity: CD16+ ($p < 0.05$) and CD56+ cells ($p < 0.01$)	[30]
Lack of data	45 patients with malignant tumors (20 controls) – levels of IL-2 and NK cell activity significantly increased in study group ($p < 0.01$)	[31]
RCT (phase II)	51 patients with malignant neoplasm, 48 healthy controls – significant increase in the level of CDT3+, CDT4+, CDT8+ cells in acupunctured group	[32]
Lack of data	40 patients with malignant tumors (20 controls), acupunctured group exhibited: – increased level of T lymphocyte subsets CD3+, CD4+, CD4+/CD8+ ($p < 0.01$) – increase in β -endorphin serum concentration ($p < 0.01$) – decreased level of soluble interleukin-2 receptor ($p < 0.01$)	[33]

NK – natural killer; IFN- γ – interferon γ ; IL-2 – interleukin 2; RCT – randomized controlled trial; CD – cluster of differentiation

formed cells may additionally facilitate formation of antigen material derived from decomposing tumour cells, which, in turn, induces development of the secondary, adaptive immune response by DCs and T lymphocytes [11].

There is also suggestion that acupuncture works through the regulatory pathway of the *Spi-1* proto-oncogene (*SPI1*). *SPI1* encodes PU.1 transcription factor that masters the process of proliferation and maturation of the hematopoietic system cells [21]. To be more specific, it plays a special role in stem cells stimulation in the bone marrow and increases the number of mature NK cells [22]. In an experimental study carried out on animals, acupuncture has been found

to induce an increase in the expression of *c-Jun* gene, which is a co-activator of PU.1 [11, 23]. This finding suggests that acupuncture might work through the PU.1 pathway to regulate NK cells proliferation [23, 24].

Table 1 summarizes possible immunomodulating effects of acupuncture. Table 2 presents studies exemplifying acupuncture's role in stimulating the immune system.

The acupuncture's anticancer effect

In Table 3 research concerning acupuncture's possible direct antitumor activity was collected. Most of the

Table 3. Studies concerning acupuncture as anticancer treatment.

Study type	Results	Ref.
Case series	patients with superficial tumors underwent electroacupuncture: – 123 were CR – 129 were PR – 36 with their tumor shrunk by 1/4 – 32 – no change in tumor size was observed The ORR (CR + PR) was 78.7%	[34]
Case series	106 patients with liver cancer – the ORR was the highest (73.7%) in the group where both electroacupuncture and liver artery intubation chemotherapy were performed – the other two groups of either electroacupuncture or liver artery intubation chemotherapy presented with ORR of 55.6% and 28.1% respectively	[35]
Case series	Omura's ST36 point stimulation: – decrease in cancer cell telomere, integrin $\alpha 5\beta 1$ and oncogen C-fos Ab2 expression	[36]
Case report	52-year-old woman with DCIS – regression of DCIS after treatment with acupuncture	[37]
Animal model	Mice with transplanted mammary cancer – acupunctured group exhibited less tumor volume ($p < 0.01$) – higher lymphocytic infiltration degree of tumor ($p < 0.05$)	[9]
Animal model	Liver cancer, gastric cancer and hypodermic tumor rat models were obtained by implantation of replicated Walker-256 cell strain. – the gross tumor volume in electroacupunctured group was significantly smaller than in control group ($p < 0.05$)	[38]
Animal model	Mice with implanted osteosarcoma – stimulation of ST36 acupoint: – twice weekly beginning at postimplantation day 3: reduction in tumor growth, tumor lymphatics, vasculature and innervation; marked reduction in pulmonary metastasis – twice weekly starting at postimplantation day 7: significant increase in tumor growth	[39]
Animal model	Mice with inoculated Lewis lung carcinoma – group of acupuncture combined with paclitaxel presented significantly lower tumor mass than in both groups where either acupuncture or medication was applied	[40]
Systematic review and meta-analysis	– enhancement of immediate tumor response	[41]

CR – complete remission; PR – partial remission; ORR – overall response rate; DCIS – ductal carcinoma in situ

referred studies were conducted on animal models. The majority of the authors suggest that this method can effectively diminish tumor volume [9, 34, 37–39]. Also, some papers point to its potential application as additional therapy to the classic anticancer treatment [35, 40]. One trial presents some of the molecular effects of acupoint stimulation, which were suggested to inhibit cancer cell activity [36]. It is essential to notice that results of one of the analyzed studies exhibited two opposite effects of acupoint stimulation, depending on the day of acupuncture initiation following transplantation of cancer cell into animal organism [39]. That, despite being the only report to be found to present tumor activity stimulation, can imply that the mechanism of acupuncture is still not being properly explicated, thus cannot be trusted enough to be introduced into clinical setting.

Reliability of the studies

The major problem of the research concerning antitumor activity is that it is scant. Although the results of the majority of presented studies are promising, some of them lack such elements as detailed methodology description, sufficient number of subjects, group characteristics or sta-

tistical significance of results, which makes it difficult to assess and compare. Moreover, the alarming pro-cancer effect revealed in one of the referred studies indicates that due to the inconsiderable amount of data, further well-designed research is required.

Summary

Since recent studies have brought about a significant progress in immunotherapy of malignant tumours, the strategy of implementing acupuncture into clinical setting, based on its immunostimulating potential, seems promising [42]. However, as of today the potential combined use of this therapy with tumour immunotherapy in order to increase the efficacy of anticancer treatment can be seen only as an experimental approach. Both the quantity and the quality of data that is available for now require improvement and further scientific attempt in this field is needed.

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